Response to Restriction Requirement

In response to the Restriction Requirement, Applicants provisionally elect, with traverse, Group II, Claims 13-20, 29 and 34-36, drawn to compounds of Formula I where only two of B, D, and E are nitrogen, a pharmaceutical composition thereof, and a metabolite thereof; claims 37-40 and 42, drawn to a method of modulating the *in vivo* activity of a kinase; claim 41, drawn to a screening method for a p70S6 kinase modulator; and claim 43, drawn to a method of inhibiting abnormal metabolic activity in a cell.

The Applicants traverse the restriction for the following reason: Claim 1 is generic. Accordingly, pursuant to MPEP §§ 803.02 and 809, the Applicants respectfully request the Office expand examination of the claims to the non-elected portion of the generic claims, which, in the present instance, is the full scope of all claims.

As stated in MPEP § 809,

> There are a number of situations which arise in which an application has claims to two or more properly divisible inventions, so that a requirement to restrict the claims of the application to one would be proper, but presented in the same case are one or more claims (generally called 'linking' claims) which, if allowable, would require rejoinder of the otherwise divisible inventions. See MPEP § 821.04 for information pertaining to rejoinder practice. . . . The most common types of linking claims which, if allowable, act to prevent restriction between inventions that can otherwise be shown to be divisible, are (A) genus claims linking species claims . . . . The linking claims must be examined with, and thus are considered part of, the invention elected. When all claims directed to the elected invention are allowable, should any linking claim be allowable, the restriction requirement must be withdrawn. Any claims(s) directed to the non-elected invention(s), previously withdrawn from consideration, which depends from or requires all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability.

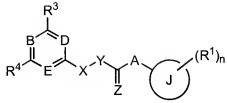
M.P.E.P. § 809 (emphasis added).

The applicants have the right to define what they regard as their invention, so long as their claims otherwise satisfy the statutory requirements. *In re Harnisch*, 206 U.S.P.Q. 300, 305 (C.C.P.A 1980). Applicants have the right to have each claim examined on the merits. *In re Weber et al.*, 198 U.S.P.Q. 328, 331 (C.C.P.A. 1978). Restriction of the subject matter of a single claim in a patent application is therefore generally impermissible because it denies the applicant the right to have that claim examined on the

merits. *Id.* As the court stated in Weber, if "a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits." *Id.* Accordingly, "it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention." M.P.E.P. § 803.02.

The claims are written in Markush format. A Markush grouping is proper if the compounds in the Markush group share a single structural similarity and a community of properties (e.g., a common utility), such that the grouping is not repugnant to the principles of scientific classification. *Harnisch*, 206 U.S.P.Q. at 305; *Ex parte Brouard et al.*, 201 U.S.P.Q. 538, 540 (Bd. Pat. App. & Int. 1976). In other words, "unity of invention exists where compounds share a common utility, and (2) share a substantial structural feature essential to that utility." M.P.E.P. § 803.02. The fact that the compounds in a Markush group may require different fields of search does not render the Markush group improper. *Brouard*, 201 U.S.P.Q. at 540. Also, where a Markush expression is applied only to a portion of a chemical compound, the propriety of the grouping is determined by consideration of the compound as a whole, and does not depend on there being a community of properties among the members of the Markush expression. *Id*; *Harnisch*, 206 U.S.P.Q. at 305; M.P.E.P. § 2173.05(h). In *Harnisch*, 206 U.S.P.Q. at 305, and as it is applied in *Ex parte Hozumi*, 3 U.S.P.Q.2d 1059 (Bd. Pat. App. & Int. 1984), the determinative factor for determining whether or not a Markush group is proper was held to be whether there existed "unity of invention," or rather whether the claims were drawn to a collection of unrelated inventions. Specifically, the claims in *Harnisch* were drawn to a class of substituted coumarin compounds disclosed as being "useful as dyestuffs." 206 U.S.P.Q. at 305. Accordingly, all of the claims had in common a functional utility related to a substantial structural feature disclosed as being essential to that utility.

Applicants submit that all pending claims 1-43 possess unity of invention. First, all of the compounds share a common utility as p70S6 kinase inhibitors. Second, each of the compounds in the Markush group share common structural features that contribute to their activity. Each of the compounds share the following significant structural features:



where the ring containing B, D and E is a nitrogen containing heteroaryl moiety, and the J ring is an aromatic moeity. Accordingly, all of the compounds read upon claims that share common utility and structural features essential for that utility.

In view of the foregoing, the applicants submit that the claims are proper Markush claims and should be examined fully on their merits as generic linking claims for the elected group. To do otherwise would infringe on Applicants' "right to have each claim examined on the merits." *Weber*, 128 U.S.P.Q. at 331.

The proper procedure for examining Markush claims is provided in M.P.E.P. § 803.02:

> A Markush-type claim may include independent and distinct inventions. ... In applications containing a Markush-type claim that encompasses at least two independent or distinct inventions, the examiner may require a provisional election of a single species prior to examination on the merits. ... Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable, the provisional election will be given effect and examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.
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> * * *
>
> On the other hand, should the examiner determine that the elected species is allowable, the examination of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a *nonelected species*, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The examination will be extended to the

extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action can be made final unless the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p).

Pursuant to MPEP 803.02 and 809, the entire scope of the claims must be examined.

REMARKS

In this amendment, Applicants have currently amended claims 13, 37, 39, and 43, and have currently cancelled claim 38, for the sole purpose of expediting prosecution. Applicants preserve the right to prosecute all cancelled claims and deleted subject matter in continuing patent applications.

Rejections under 35 U.S.C. § 112

(1) The Office rejected claims 37-43 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not reasonably provide enablement for modulating *in vivo* activity of a kinase (claim 37), where the kinase is p70S6 (claim 38), by inhibiting p70S6K (claim 39), to a treat disease or disorder associated with uncontrolled, abnormal or unwanted cellular activities (claim 40), to screen for a p70S6 kinase modulator (claim 411), to inhibit proliferative activity (claim 41) or inhibit abnormal cell metabolic activity (claim 43). Applicants respectfully traverse this rejections.

The Legal Standard for Enablement

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.q.2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. *See Hybritech Inc., v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art"). The determination of enablement is based on whether a person skilled in the pertinent art could make and use the invention without undue experimentation. *See Northern Telecom, Inc. v Datapoint Corp.*, 908 F.2d 931 (Fed. Cir. 1990). The applicant(s) for a patent application need no set forth every minute detail regarding the invention. *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991).

Undue experimentation is experimentation that would require a level of ingenuity beyond from what would be expected from one of ordinary skill in the art. *Fields v.*

Conover, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The fact that experimentation may be complex does not make it undue, so long as the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174. The factors that may be considered in making a determination of whether an amount of experimentation is undue are listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the breadth of the claims, the level of predictability in the art, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature, and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Further, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals in *In re Angstadt,* has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue. In particular, in an unpredictable art, it is not necessary for an inventor to disclose a test with every species covered by a claim, as it would force an inventor seeking patent protection to carry out a prohibitive number of experiments, which could discourage inventors from filing patent applications in technical areas that may be unpredictable. In re Angstadt, 190 U.S.P.Q. 214(C.C.P.A. 1976).

In regard to Claim 36, Applicants have deleted claim 36, thereby rending the rejection of this claim moot. Applicants respectfully request reconsideration and withdrawal of this rejection.

The specification fully enables Claims 37 and 39, which relate to a method of modulating *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of a composition comprising a compound according to claim 13, wherein the kinase is p70S6K (claim 37 as amended), and wherein the modulation of p70S6K can be the inhibition of p70S6K (claim 39 as amended). Applicants respectfully point out that there are many specific compounds in claim 34 that support the generic

scope of claim 13, and these compounds were tested to be active in modulating (inhibiting) p70S6K in terms of their p70S6K IC_{50} values (see Table 2). In addition, p70S6K assays are described in paragraph 200, which fully enables one skilled in the art to test the p70S6K IC_{50} values for the claimed compounds.

Applicants assert that the breadth of the claims is very specific towards modulating, or inhibiting, *in vivo* activity of p70S6K. The predictability is satisfied by the numerous compounds in the claims that can modulate or inhibit p70S6K. In addition there is a lot of guidance in the specification of what compounds can be potentially used, and how to use these compounds, for the purposes of modulating, or inhibiting, *in vivo* activity of p70S6K. Each compound in claim 34 is a working example of which compounds can be used to modulate or inhibit *in vivo* activity of p70S6K. Accordingly, the specification provides enablement for amended Claims 37 and 39. Applicants respectfully request reconsideration and withdrawal of these rejections.

The specification fully enables Claim 40, which relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of a composition comprising a compound according to claim 13. As stated above, there are many specific compounds in claim 34 that support the generic scope of claim 13, and these compounds were tested to be active in modulating (inhibiting) p70S6K in terms of their p70S6K IC_{50} values (see Table 2). As stated in paragraph [0012], the enzyme p70S6K modulates protein synthesis by phosphorylation of the S6 ribosomal protein promoting translation. A role for p70S6K in tumor cell proliferation and protection of cells from apoptosis is supported based on its participation in growth factor receptor signal transduction, overexpression and activation in tumor tissues [Pene et al (2002) Oncogene 21, 6587; Miyakawa et al (2003) Endocrin J. 50, 77, 83; Le et al (2003) Oncogene 22, 484]. Clinical inhibition of p70S6K activation was observed in renal carcinoma patients treated with CCI-779 (rapamycin ester), an inhibitor of the upstream activating kinase, mTOR. A significant linear association between disease progression and inhibition of p70S6K activity was reported [Peralba et al (2003) Clinical Cancer Research 9, 2887].

Applicants assert that the breadth of the claims is very specific towards a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of a composition comprising a compound according to claim 13. The predictability is satisfied by the numerous compounds in the claims that can modulate or inhibit p70S6K, wherein compounds that can modulate or inhibit p70S6K are associated with being able to treat diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities as described above. In addition there is a lot of guidance in the specification of what compounds can be potentially used, and how to use these compounds, for the purposes of modulating, or inhibiting, *in vivo* activity of p70S6K. Each compound in claim 34 is a working example of which compounds can be used to treat diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. Accordingly, the specification provides enablement for Claim 40. Applicants respectfully request reconsideration and withdrawal of this rejection.

The specification fully enables Claim 41 that relates to a method of screening p70S6K modulators. Paragraphs [0136]-[0156] thoroughly describe how compounds described in the specification can be used in a method for screening candidate agents that bind to p70S6K receptor kinase, wherein the protein is bound to a support, and a compound is added to the assay. For instance, paragraph [0137] describes how the binding can be determined; paragraph [0141] describes what candidate agents can be; paragraph [0142] describes where candidate agents can be obtained; paragraph [0143] describes how to determine the binding of a candidate agent; paragraph [0144] describes the labeling of a candidate agent; paragraph [0145] describes the incubation period for optimal activity; paragraphs [0146] and [0147] describe different embodiments of combining candidate agents and competitors; and later paragraphs describe controls, reagents that can be used, etc.

Applicants assert that the breadth of the claims is very specific towards a method of method of screening p70S6K modulators. The predictability is satisfied by the

numerous compounds in the claims that can modulate or inhibit p70S6K which can be used in these screening methods. In addition there is a lot of guidance in the specification of how the screening methods can be carried out, as described above. Each compound in claim 34 is a working example of which compound can be used in these screening methods. Accordingly, the specification provides enablement for Claim 41. Applicants respectfully request reconsideration and withdrawal of this rejection.

The specification fully enables Claim 42, which relates to a method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of: the compound according to claim 13. As stated above, there are many specific compounds in claim 34 that support the generic scope of claim 13, and these compounds were tested to be active in modulating (inhibiting) p70S6K in terms of their p70S6K IC_{50} values (see Table 2). As stated in paragraph [0012], the enzyme p70S6K modulates protein synthesis by phosphorylation of the S6 ribosomal protein promoting translation. A role for p70S6K in tumor cell proliferation and protection of cells from apoptosis is supported based on its participation in growth factor receptor signal transduction, overexpression and activation in tumor tissues [Pene et al (2002) Oncogene 21, 6587; Miyakawa et al (2003) Endocrin J. 50, 77, 83; Le et al (2003) Oncogene 22, 484]. Clinical inhibition of p70S6K activation was observed in renal carcinoma patients treated with CCI-779 (rapamycin ester), an inhibitor of the upstream activating kinase, mTOR. A significant linear association between disease progression and inhibition of p70S6K activity was reported [Peralba et al (2003) Clinical Cancer Research 9, 2887].

Applicants assert that the breadth of the claims is very specific towards a method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of: the compound according to claim 13. The predictability is satisfied by the numerous compounds in the claims that can modulate or inhibit p70S6K, wherein compounds that can modulate or inhibit p70S6K are associated with being able to inhibit proliferative activity in a cell as described above. In addition there is a lot of guidance in the specification of what compounds can be potentially used, and how to use these compounds, for the purposes of modulating, or inhibiting, *in vivo* activity of p70S6K.

Each compound in claim 34 is a working example of which compounds can be used to inhibit proliferative activity in a cell. Accordingly, the specification provides enablement for Claim 42. Applicants respectfully request reconsideration and withdrawal of this rejection.

The specification fully enables claim 43, which relates to a method of inhibiting abnormal metabolic activity in a cell, the method comprising administering an effective amount of: the compound according to claim 13. As stated in paragraph [0013], the enzyme p70S6K was found to be implicated in metabolic diseases and disorders. It was reported that the absence of P70S6K protects against age- and diet-induced obesity while enhancing insulin sensitivity [Um et al (2004) Nature 431, 200-205 and Pende et al (2000) Nature 408, 994-997]. A role for p70S6K in metabolic diseases and disorders such as obesity, diabetes, metabolic syndrome, insulin resistance, hyperglycemia, hyperaminoacidemia, and hyperlipidemia is supported based upon the findings.

Applicants assert that the breadth of the claims is very specific towards a method of inhibiting abnormal metabolic activity in a cell, the method comprising administering an effective amount of: the compound according to claim 13. The predictability is satisfied by the numerous compounds in the claims that can modulate or inhibit p70S6K, wherein compounds that can modulate or inhibit p70S6K are associated with being able to inhibit abnormal metabolic activity in a cell as described above. In addition there is a lot of guidance in the specification of what compounds can be potentially used, and how to use these compounds, for the purposes of modulating, or inhibiting, *in vivo* activity of p70S6K. Each compound in claim 34 is a working example of which compounds can be used to inhibit metabolic activity in a cell. Accordingly, the specification provides enablement for methods of inhibiting abnormal cell metabolic activity (claim 43). Applicants respectfully request reconsideration and withdrawal of this rejection.

(2) The Office rejected claims 36-43 under 35 U.S.C. § 112, second paragraph, alleging that these claims are indefinite. Applicants respectfully traverse.

In regard to Claim 36, Applicants have deleted claim 36, thereby rending the rejection of this claim moot. Applicants respectfully request reconsideration and withdrawal of this rejection.

In regard to Claims 37 and 39, these claims particularly point out and distinctly claim a method of modulating *in vivo* activity of a kinase, the method comprising administering to a subject an effective amount of a composition comprising a compound according to claim 13, wherein the kinase is p70S6K (claim 37 as amended), and wherein the modulation can be the inhibition of p70S6K (claim 39 as amended). Applicants respectfully point out that there are many specific compounds in claim 34 that were tested to be active in modulating (inhibiting) p70S6K in terms of their p70S6K IC_{50} values (see Table 2). Accordingly, claims 37 and 39 both satisfy the requirements of 35 U.S.C. § 112, second paragraph. Applicants respectfully request reconsideration and withdrawal of these rejections.

In regard to Claim 40, this claim particularly points out and distinctly claims a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities, the method comprising administering, to a mammal in need thereof, a therapeutically effective amount of a composition comprising a compound according to claim 13. As stated above, there are many specific compounds in claim 34 were tested to be active in modulating (inhibiting) p70S6K in terms of their p70S6K IC_{50} values (see Table 2). The specification describes in detail the activity of the claimed compounds and their intended effects. As stated in paragraph [0012], the enzyme p70S6K modulates protein synthesis by phosphorylation of the S6 ribosomal protein promoting translation. A role for p70S6K in tumor cell proliferation and protection of cells from apoptosis is supported based on its participation in growth factor receptor signal transduction, overexpression and activation in tumor tissues [Pene et al (2002) Oncogene 21, 6587; Miyakawa et al (2003) Endocrin J. 50, 77, 83; Le et al (2003) Oncogene 22, 484]. Clinical inhibition of p70S6K activation was observed in renal carcinoma patients treated with CCI-779 (rapamycin ester), an inhibitor of the upstream activating kinase, mTOR. A significant linear association between disease progression and inhibition of p70S6K activity was reported [Peralba et al (2003) Clinical Cancer Research 9, 2887].

Accordingly, claim 40 satisfies the requirements of 35 U.S.C. § 112, second paragraph. Applicants respectfully request reconsideration and withdrawal of this rejection.

In regard to claim 41, this claim particularly points out and distinctly claims a method of screening p70S6K modulators. As stated above, paragraphs [0136]-[0156] thoroughly describe how compounds described in the specification can be used in a method for screening candidate agents that bind to p70S6K receptor kinase, wherein the protein is bound to a support, and a compound is added to the assay. For instance, paragraph [0137] describes how the binding can be determined; paragraph [0141] describes what candidate agents can be; paragraph [0142] describes where candidate agents can be obtained; paragraph [0143] describes how to determine the binding of a candidate agent; paragraph [0144] describes the labeling of a candidate agent; paragraph [0145] describes the incubation period for optimal activity; paragraphs [0146] and [0147] describe different embodiments of combining candidate agents and competitors; and later paragraphs describe controls, reagents that can be used, etc. Accordingly, claim 41 satisfies the requirements of 35 U.S.C. § 112, second paragraph. Applicants respectfully request reconsideration and withdrawal of this rejection.

In regard to claim 42, this claim particularly points out and distinctly claims a method of inhibiting proliferative activity in a cell, the method comprising administering an effective amount of: the compound according to claim 13. As stated above, the specification describes in detail the activity of the claimed compounds and their intended effects. As stated above, there are many specific compounds in claim 34 that support the generic scope of claim 13, and these compounds were tested to be active in modulating (inhibiting) p70S6K in terms of their p70S6K IC_{50} values (see Table 2). As stated in paragraph [0012], the enzyme p70S6K modulates protein synthesis by phosphorylation of the S6 ribosomal protein promoting translation. A role for p70S6K in tumor cell proliferation and protection of cells from apoptosis is supported based on its participation in growth factor receptor signal transduction, overexpression and activation in tumor tissues [Pene et al (2002) Oncogene 21, 6587; Miyakawa et al (2003) Endocrin J. 50, 77, 83; Le et al (2003) Oncogene 22, 484]. Clinical inhibition of p70S6K activation was observed in renal carcinoma patients treated with CCI-779 (rapamycin ester), an inhibitor

of the upstream activating kinase, mTOR. A significant linear association between disease progression and inhibition of p70S6K activity was reported [Peralba et al (2003) Clinical Cancer Research 9, 2887]. Accordingly, claim 42 satisfies the requirements of 35 U.S.C. § 112, second paragraph. Applicants respectfully request reconsideration and withdrawal of this rejection.

In regard to claim 43, this claim particularly points out and distinctly claims a method of inhibiting abnormal metabolic activity in a cell, the method comprising administering an effective amount of: the compound according to claim 13. The specification describes in detail the activity of the claimed compounds and their intended effects. As stated in paragraph [0013], the enzyme p70S6K was found to be implicated in metabolic diseases and disorders. It was reported that the absence of P70S6K protects against age- and diet-induced obesity while enhancing insulin sensitivity [Um et al (2004) Nature 431, 200-205 and Pende et al (2000) Nature 408, 994-997]. A role for p70S6K in metabolic diseases and disorders such as obesity, diabetes, metabolic syndrome, insulin resistance, hyperglycemia, hyperaminoacidemia, and hyperlipidemia is supported based upon the findings. Accordingly, claim 43 satisfies the requirements of 35 U.S.C. § 112, second paragraph. Applicants respectfully request reconsideration and withdrawal of this rejection.

Applicants respectfully request that the present amendments and remarks be entered and made of record in the instant application. Withdrawal of the Examiner's rejections and allowance of this patent application is respectfully requested. The Examiner is invited to telephone the undersigned to discuss any remaining issues in connection with this patent application.

Respectfully submitted,

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